CORRESPONDENCE

THE PARADOX OF NALOXONE

Sir,—In their recent editorial Smith and Pinnock (1985) mentioned the fact that, although naloxone has been traditionally regarded as a pure opioid antagonist without agonist activity, evidence has accumulated that this may not be so. Later in the editorial, they opine that these apparently paradoxical actions of naloxone have now become explicable on the basis of the endogenous opioid peptide system—although some of its actions await clarification. However, the only theoretical explanation offered in the article for these effects is the differential sensitivity of the various opioid receptors to naloxone, with the latter being more active at mu than at delta and kappa sites. In view of the dearth of references given to this, possibly most important, paradoxical effect of naloxone we would like to refer to some of our own work on this topic.

To our knowledge we were the first to publish specifically on this paradoxical effect in human subjects in which naloxone was shown to both inhibit and enhance nitrous oxide analgesia in different subjects (Gillman, Kok and Lichtigfeld, 1980; Gillman and Lichtigfeld, 1981). In these papers we explained this unexpected analgesic effect of naloxone in terms of the existence of two opposing opioid systems, one analgesic and the other hyperalgesic—each having differential sensitivities to naloxone. Before our work Lasagna (1965) had noted an analgesic effect of naloxone at low doses, but did not investigate this observation further, most probably because it predated the discovery of the endogenous opioid system.

We have expanded our understanding of this phenomenon in a paper published recently (Gillman and Lichtigfeld, 1985) in which a great deal of independent confirmatory evidence is provided for the presence of two opposing opioid systems involved in pain processing, one being analgesic and the other hyperalgesic. Anatomical evidence for the hyperalgesic system postulated by us has been provided by Wu and colleagues (1983). Furthermore, these two systems may well play a part in other physiological processes and disease states, viz. cardiovascular homeostasis (Petry and de Jong, 1983), addiction (Gillman and Lichtigfeld, 1984), feeding behaviour (Gillman and Lichtigfeld, 1986), sexual behaviour (Gillman and Lichtigfeld, 1983) and ictal phenomena (Urca, Yitzhaky and Frenk, 1981).

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REFERENCES


NALOXONE — FRIEND OR FOE?

Sir,—Naloxone has attracted much recent attention because of its ability to produce arousal in non-opioid induced coma states. The arousal response may be so extreme as to produce many untoward effects and it has been suggested that naloxone should be used with caution (Smith and Pinnock, 1985). I would like to propose another reason for care in the use of naloxone as illustrated by a recent patient.

A 63-year-old man (ASA Class II) underwent surgery for recurrent squamous cell carcinoma of the nasal septum and ethmoid sinus. During surgery the brain was inadvertently entered, but the trauma was considered minor and the patient remained stable, subsequently to be transferred to the recovery room. He was noted to be drowsy, but otherwise his observations were normal. After 2.5 h in recovery he was still drowsy and so naloxone was administered to antagonize the narcotic which had been given during the operation. The patient responded immediately, became alert and started talking. The medical staff present all interpreted this as substantiating their diagnosis of narcotic “overdose” and left instructions for the resident staff to give further doses of naloxone as required. He received two further doses of naloxone which did not improve his condition markedly but, since his vital signs remained stable, no further action was taken until 7 h after his arrival in the recovery room. At this time a full neurological examination was undertaken because of his persistent somnolence. The CT scan revealed a subarachnoid haemorrhage with intraparenchymal blood under the Sylvian fissure, and blood in the ventricles with hydrocephalus. He was managed conservatively and his mental status returned to normal by the 2nd day after operation.

It is possible that, in this patient, the arousal response produced by the naloxone was mediated by improved cerebral blood flow to ischaemic brain rather than by opioid
antagonism. It is certainly true that the response induced a "false sense of security" within the medical staff as to the aetiology of the sedation and increased the delay before its full investigation.

The message is clear that, when evaluating a patient with unexpected sensory depression or frank CNS symptomatology, consideration must be given to the same diagnoses that would be entertained had the finding occurred independent of a temporal relationship to a recent anaesthetic. Particular care should be exercised in the interpretation of a positive response to naloxone as being diagnostic of narcotic overdosage.

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REFERENCE

HYPOACOUSIS FOLLOWING EXTRADURAL INJECTION
Sir,—Three patients have been observed in whom acute loss of auditory acuity (hypoacousis) occurred at the end of the injection of local anaesthetic solution to the lumbar extradural space. A standard technique was used. Puncture was performed at L2-3 using loss of resistance to saline; an extradural catheter was inserted. A test dose of 2% lignocaine 4 ml was injected through the catheter. In no patient were there neurological or cardiovascular symptoms to suggest i.v. injection.

Patient 1 was a 59-yr-old man undergoing metatarsal osteotomies of the right foot. After the injection of the main dose of 2% lignocaine 16 ml with adrenaline, he complained that he felt that someone had placed cotton wool in his ears. The hypoacousis lasted for 10 min before return to normal hearing. Anaesthesia was obtained to T6.

Patient 2 was a 34-yr-old primigravida in labour. After the injection of 0.5% bupivacaine 8 ml she complained that her ears had become blocked. The hypoacousis lasted for 5 min before return to normal. Analgesia was obtained to T9. Subsequent "top-ups" of the same dose were uneventful.

Patient 3 was a 25-yr-old primigravida undergoing Caesarean section. An injection of 2% lignocaine 16 ml with adrenaline was given. At the end of this she complained of "fullness" in her head, accompanied by the feeling that her ears had become blocked. The sensation of fullness in the head lasted some 30 s, but the hypoacousis persisted for almost 10 min. Anaesthesia was obtained to T5 and the Caesarean section progressed uneventfully.

Injection of fluid to the extradural space gives rise to feelings of fullness in the head as a result of a concomitant increase in intracranial pressure (Burn, Guyer and Langdon, 1973). There is free communication across the cochlear aqueduct between cerebrospinal fluid and the perilymph of the cochlear apparatus (Warwick and Williams, 1973). Changes in CSF pressure are therefore accompanied by changes in cochlear perilymph pressure. The position of the hair cells and basement membrane of the cochlear apparatus is determined by the relative pressures in the perilymph (equals CSF pressure) and the endolymph (active secretion). Post-spiral hypoacusis has been reported in which a decrease in CSF pressure produces a distortion of the structures by pressure imbalance and gives rise to damping of the response to auditory stimuli (Gordon, 1983; Panning, Mehler and Lennhardt, 1983). It is possible, therefore, that the hypoacusis following injection of fluid to the extradural space is a consequence of the increase in perilymph pressure which accompanies the increase in CSF pressure. It is important to differentiate symptoms resulting from the mechanical effect of injection from those caused by intravascular injection of local anaesthetic.

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REFERENCES


PROLONGED APNOEA WITH KETAMINE
Sir,—Ketamine is used all over the world, frequently in minor procedures involving children. In the developing countries anaesthetics are usually administered by nurses or auxiliaries and ketamine, as well as ether, is frequently used. However, because of its reputation for general safety, support of the circulation and lack of respiratory depression, relatively little attention is paid to the vital functions during its use (Philips et al., 1970). This is understandable, since medical officers usually operate under primitive circumstances, in undernourished hospitals and with relatively poorly trained personnel (van Wijhe, 1981). Although the use of ketamine presents few problems in the majority of patients, it is a drug with potentially serious adverse effects (Austin and Bevan, 1971). Since we have treated a child who developed prolonged apnoea despite use of the recommended dose and standard procedures (Gregory, 1983), we advise that adequate means of artificial ventilation be at hand when ketamine is used.

A 4-month old girl was scheduled for an EMG, a cervical myelography and a CT scan of the cervical spinal cord for investigation of a brachial plexus injury obtained at birth. Her weight was 6.3 kg, her birth had been at term, and a general physical examination showed no other abnormalities (notably, no signs of increased intracranial pressure). She was not receiving any drug(s). As the expected duration of the investigations was 1.5–2 h we decided to intubate the trachea so as to be able to assist the respiration when necessary. A premedication of pentobarbitone 25 mg rectally was given 2 h before the induction of anaesthesia, which consisted of ketamine 60 mg i.m. (10 mg/kg body weight), oxygenation by facemask, placement of an i.v. catheter, atropine sulphate 0.12 mg i.v. and suxamethonium 12 mg i.v. Oral intubation with a 3.5-mm diameter tracheal tube (without cuff) was uneventful; auscultation of the lungs confirmed the correct position of the tube. Oxygen was given with the Jackson–Rees non-rebreathing system. Because of some movement 15 min after the i.m. dose, an additional ketamine 10 mg was administered slowly i.v., and the investigator was requested to